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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/938,160	08/23/2001	Clark M. Whitehead	P-191	1257

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EXAMINER
KIM, VICKIE Y

ART UNIT	PAPER NUMBER
1614	6

DATE MAILED: 07/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/938,160	WHITEHEAD ET AL.	
	Examiner	Art Unit	
	Vickie Kim	1614	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30,38 and 39* is/are pending in the application.

4a) Of the above claim(s) *6-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 38-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election acknowledged

1. Applicants affirmation on the election with traverse of Group I, claims 1-5 is acknowledged. Applicant partially traversed the restriction requirement on the grounds that there would be no patentably distinct invention. This argument is partially persuasive and thus, applicant's request is partially accepted and thus, groups I and III are taken together for the examination. A mentioned in previous office acition, as not all groups encompassed by the application would be classified together. Furthermore, each invention is found to be patentably distinct subject matter proven in numerous patent literatures. Claims I and II are directed to a method of treating scleroderma using PDE2 inhibitor or the claimed formula, respectively. Even the structure of the compounds having PDE2 inhibitory activity(=PDE2 inhibitor) can be different from one to another. Furthermore, the claimed compound found in Groups I and II do not have common features. For instance, dipyridamole(PDE2 inhibitor) has different structure than the compound of formula found in claim 6, and would be claissified differently.

Thus, the claimed subject matter of groups I and II are patentably distinct and thus, the restrictioin deems proper. Furthermore even if there were unity of classification, the search of the entire application in patent and non-patent literature (a significant part of the thorough examination) would be burdensome due to the reasons mentioned in previous office action(e.g. patentably distinct subject matter proven in numerous patent literature). Therefore the restriction requirement is maintained and made FINAL.

Information Disclosure Statement

The supplemental information disclosure statement (IDS) submitted on 11/25/03 was acknowledged. The information disclosure statement is being considered by the examiner. Please refer to Applicant's copy of the 1449 submitted herewith.

However, the information disclosure statement(IDS) submitted on 09/05/2001 fails to include the listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." It is noted to applicant that the examiner finds one page(looks like first page) of IDS dated 09/05/2001. In the case where IDS(PTO-1449 and copies of references) submitted had been lost during the process of entering and delivering the papers, applicant is advised to resubmit the IDS with a proof showing the proper filing with all the necessary information submitted to PTO.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "subtantially" in claims 1 is a relative term which renders the claim indefinite. The term "subtantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-4 and 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Au-Young et al(US 6,080,548) in view of Weinstein et al (US 6,569,638), Lugnier(1992, abstract only) and Greenwald(1979, abstract only).

Claims are drawn to a method of treating scleroderma using an effective amount of PDE2 inhibitor that does not inhibit COXI or COXII.

US'548 teaches that dipyridamole(an inhibitor of PDE 5 and PDE 8) is effectively used in the treatment of sclerodermaImmune disorder) and cancers,see column 12, lines 35 –36 and column 21, lines 56.

Applicant's claims differ in that they require a PDE2 inhibitor and substantially no inhibition of COXI or II.

Weinstein et al(US'638) teaches a method of treating neoplasia using a compound wherein the compound exhibit phosphodiesterase(PDE) inhibition, activating

JNK kinase, growth inhibition and apoptosis induction which is responsible for the therapeutic effectiveness for. treating neoplasia, see abstract. It further teaches that dipyridamole activates JNK and PDE2/5 inhibiting activity. see column 7, lines 1026.

The PDE2 inhibitory activity of dipyridamole(10um) in addition to PDE5 inhibitory activity is also proven and evidenced by Lugnier(abstract only, 1992). Lugnier is particularly pertinent to the claimed subject matter beacuase Lugnier teaches that dipyridamole is potent PDE 2 inhibitor, see abstract.

Greenwald teaches that dipyridamole does not inhibit cyclooxygenase(COX), see abstract.

Thus, it would have been obvious to use dipyridamole to treat scleroderma when these references are combined because the deficiency found in US'548 is taught by the latter references. Although PDE2 inhibitory activity and substantially no COX inhibitory activity are possessed by dipyridamole(PDE 5 inhibitor) inherently, said activity is assured by the teaching of Weinstein et al. , Lugnier and Greenwald.

One would have been motivated to combine the references because the treatment could be carried out with assurance wherein a compound with cyclooxygenase inhibitory activity is well known for its side effect (e.g. gastric irritation).

4. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Au-Young et al in view of Weinstein et al , Lugnier and Greenwald, as applied to claims 1-4 and 38-39 above, and further in view of Pamukcu et al(US'547).

The teaching of AU-Young et al in view of Weinstein, Lugnier and Greenwald is mentioned immediately above in 103 rejection(supra).

Applicant's claim differs in that it require the IC50 value for PDE2(i.e. less than 25um) enzyme and COX(greater than 40uM) enzyme .

Pamukcu also teaches that improved treatment can be achieved by selecting specific PDE2/5 inhibitors having substantially no COX inhibitiory activity. In other words, PDE 5 inhibitors without PDE2 inhibitory activity fails to show antineoplastic activities, see column 6, especially lines 20-22. Furthermore, Pamukcu et al (US'547) teach generically about a PDE2/5 inhibitor that has the IC50 value less than 10uM and its antineoplastic properties wherein IC50 value less than 10uM is indicative for antineoplasia properties, see column 17. Pamukcu et al also teaches the unwanted side effects due to COX inhibition and how to assay the COX inhibitory activity which could be used in screening process.

Although Pamukcu et al does not specifically mention about dipyridamole, it would have been obvious to one of ordinary skill in the art at the time the invention was made to conclude that dipyridamole's IC50 value for PDE2 and COX is well within the range that results in antineoplastic activities without COX inhibition, that is IC50 value of less than 10um for PDE and IC50value of greater than 40um when these cited references are taken together because dipyridamole which is known to be potent PDE2 inhibitor and has antineoplasia activities without COX inhibition(mentioned in 103 rejection above,) would have meet the criteria inherently. The techniques for how to obtain IC50 value and assay COX inhibition are considered to be conventional and also well taught by the cited reference(Pamukcu).

One would have been motivated to use PDE2/5 inhibitor(e.g. dipyridamole) without COX inhibition for treating various disorders such as scleroderma and cancers because said inhibitor has potent therapeutic effectiveness but reduces side effects associated with COX. Since it's effectiveness and safety is well proven, one would have motivated to select PDE2/5 inhibitors to treat scleroderma, with assurance and reasonable expectation of success when these references are combined because a PDE 2/5 inhibiton with substantially no COX inhibition would be most desirable therapeutic modalities because compliance is one of most critical factor to achieve the successful treatment.

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same (or similar) ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Conclusion

5. No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vickie Kim whose telephone number is 703-305-1675. The examiner can normally be reached on Tuesday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on 703-308-4725. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-3165 for regular communications

and 703-746-3165 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Vickie Kim,
Patent examiner
June 27, 2003
Art unit 1614